The Egyptian Journal of Hospital Medicine (April 2024) Vol. 95, Page 1795- 1800

Trial of Topical Tacrolimus by Two Different Concentrations in Treatment of Nail Psoriasis: Randomized Comparative Study

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ABSTRACT

Background: Nail affection is estimated to affect about 85% of cases with psoriasis vulgaris (PV) in their lifetimes and is frequently accompanied by severe disease and impairment of quality of life (QoL). Tacrolimus (0.1-0.03%) ointment was demonstrated to be efficient in PV owing to its immunosuppressive characteristics. Regarding its therapeutic effect on nail psoriasis (NP), it appeared to be similarly efficient on nail bed and matrix lesions without having extensive adverse events**.**

Objectives: Since previous trials on topical tacrolimus in treatment of NP was concentrating only on the higher concentration (0.1%), which is more expensive and frequently not available in many developing countries, the present study aimed to evaluate and compare the efficacy and safety of topical tacrolimus by the two concentrations (0.1% and 0.03%) in treatment of nail psoriasis.

Patients and Methods: This randomized comparative study comprised 50 patients with nail psoriasis; half of them were treated by tacrolimus 0.1% (group A) and the other half by tacrolimus 0.03% (group B). Five patients from each group were lost follow up so the statistics involved only 20 cases in each group, the assessment of disease severity was conducted by using Nail Psoriasis Severity Index (NAPSI) score.

Results: There was a statistically significant decrease in NAPSI score starting 1 month after initiation of treatment in both groups. Although improvement frequency was better in group A than group B but the difference was not statistically significant.

Conclusion: both concentrations of topical calcineurin inhibitors (0.1% and 0.03%) showed high statistically significant improvement in NP after six months of treatment. Additionally topical calcineurin inhibitors demonstrated no side effects, so they are safe and tolerable drugs in the context of NP treatment.

Keywords: Nail Psoriasis, NAPSI, Tacrolimus 0.1%, Tacrolimus 0.03%

INTRODUCTION

Patients with nail psoriasis (NP) have impaired quality of life (QoL) owing to the appearance of nails, and considerable morbidity and functional impairments. The proper treatment is difficult as a complete cure takes much time, and in several cases, it is not satisfying with subsequent deterioration [(1)].

Psoriatic nails might illustrate different features conforming to the structure concerned within the nail unit. Leukonychia, dystrophy, and irregular nail pitting are symptoms of nail matrix affection. Onycholysis, subungual hyperkeratosis, splinter hemorrhages, and nail thickening are the outcomes of nail bed affection. In addition, the periungual area may be impacted by PV, leading to psoriatic paronychia [(2,3)].

A complete cure for psoriatic nails is difficult, and the efficiency of different therapeutic modalities remains under investigation. Due to the distinctive anatomy of the nail, it is impossible to reach efficient concentrations of local agents in all nail components [(4)].

The calcineurin inhibitor tacrolimus demonstrates better skin and nail penetration. It revealed good activity on nail bed as well as on matrix PV [(5)].

Although topical and systemic therapy of psoriatic nails have been widely studied, few studies have tried to assess the efficacy of topical calcineurin inhibitors on psoriatic nails [(5)].

Aim of the work

The bulk of the studies of topical tacrolimus in treatment of NP were concentrating on the higher topical concentration (0.1%), which is more expensive and frequently not available in many developing countries. Our study aimed to evaluate and compare the two concentrations (0.1% and 0.03%) of topical tacrolimus ointment in treatment of nail psoriasis as regard efficacy, safety and patients' satisfaction**.**

PATIENTS AND METHODS

This is a randomized comparative study that was conducted at Outpatient Clinic of Dermatology Department, Mansoura University Hospitals.

Fifty patients with NP (Diagnosis was according to the typical presentation of NP) were comprised in this study. Only forty patients completed the study (as 10 patients were lost during the follow up). The cases were haphazardly divided into two equal groups: group A (=20 cases) treated by (Tacrolimus 0.1%, protopic ointment 0.1% from LEO company) and Group B (= 20 cases) treated by (Tacrolimus 0.03% from Al Andalous for Pharmaceutical Industry, Egypt) to assess improvement in both groups.

The age range was from 1 to 60 year.

Inclusion criteria: All patients presenting with nail disease coincide clinically with psoriasis.

Received: 21/11/2023
Accepted: 22/01/2024

Exclusion criteria:

- Patients assuming systemic therapy approved for PV in the three months before enrolment in the study.
- Patients taking topical treatment for nail psoriasis in the preceding three months.
- Patients with onychomycosis.
- Patients refusing the study.

The cases were subjected to the following; history taking (such as the demographic data and history of current illness) and physical examination to evaluate nail lesion.

Tacrolimus was applied twice daily onto the nail folds and nail plate of the affected nails without occlusion or transdermal delivery systems. After the bedtime application, the cases were informed not to wash their hands until the morning of the following day. Application was continued for six months or until complete improvement.

Clinical examination was performed by the authors every month for six months. Photo was taken during every visit for follow up.

Assessment of the Disease severity

Severity of NP was assessed at baseline and then monthly for six months using NAPSI score by the same dermatologist.

Nail lesions were scored based on NAPSI. Typically, the nail is divided into four quadrants. Entire NP-related symptoms in the nail matrix (pitting, leukonychia, red patches in the lunula and crumbling nail plate) and nail bed (onycholysis and hyperkeratosis) are measured and scored in the NAPSI. For fingernails, the total NAPSI scores range from 0 to 80 [(6)]. Response to treatment was assessed by photographic photos every month for 6 months.

Ethical approval

The study was conducted according to Helsinki Standards as revised in 2013 after obtaining the approval from the Ethics Committee, Faculty of Medicine, Mansoura University and a written informed consent was obtained from all adult comprised patients and all caregivers of juvenile patients.

Statistical analysis

Data analysis was conducted by SPSS software, (PASW statistics for windows version 25. Chicago: SPSS Inc.). Qualitative data were evaluated by utilizing number and percent. Quantitative data were evaluated by utilizing median and range for non-normally distributed data and mean±SD for normally distributed data, following assessing normality using Shapiro Wilk test. Chi-Square, Fisher exact tests, and Monte Carlo test were utilized to compare qualitative data between groups. Mann Whitney U test was utilized to compare between the two studied groups for non-normally distributed data. In terms of all the previously utilized tests, p was considered significant when its value was less than 0.05.

RESULTS

Table (1) displays that there was no statistically significant difference between the studied groups concerning age, sex, occupation, smoking history and family history among studied groups.

Table (1): Sociodemographic characteristics of the studied cases.

	Group A		Group B		Test of significance
	N=20	%	N=20	%	
Age/ years Median (min-max)	18(1-62)		32.5(2-60)		Z=1.03 P=0.304
Sex Male Female	 12 8	 60.0 40.0	 7 13	 35.0 65.0	 χ^2=2.51 P=0.113
Occupation Housewives Not working Manual worker Employee Professional worker	 3 11 4 0 2	 15.0 55.0 20.0 0.0 10.0	 9 5 3 1 2	 45.0 25.0 15.0 5.0 10.0	 MC=6.39 P=0.172
Special habits No Smokers	 18 2	 90.0 10.0	 16 4	 80.0 20.0	 χ^2=0.784 P=0.376
Family history -ve +ve	 19 1	 95.0 5.0	 17 3	 85.0 15.0	 χ^2=1.11 P=0.292

Z: Mann Whitney U test, MC: Monte Carlo test, χ^2; Chi-Square test

Table (2) illustrates that there was no statistically significant difference between the studied groups as regard presence of skin lesion and presence of medical co-morbidities and presence of psoriatic arthropathy.

Table (2): Skin disease and disease duration distribution among studied cases

	Group A		Group B		Test of significance
	N=20	%	N=20	%	
Skin lesion No Yes	 7 13	 35.0 65.0	 3 17	 15.0 85.0	 χ^2=2.13 P=0.144
Medical co-morbidities -ve +ve	 16 4	 80.0 20.0	 12 8	 60.0 40.0	 χ^2=1.91 P=0.168
Psoriatic arthropathy	3	15.0	7	35.0	χ^2=2.13 P=0.144
Disease duration (years) Median (min-max)	 2.5(0.08-20)		 3.0(0.17-30.0)		Z=0.449 P=0.653

Z: Mann Whitney U test, MC: Monte Carlo test, χ^2; Chi-Square test

Table (3) demonstrates a statistically significant higher frequency of nail crumbling among group A than group B, also statistically significant higher frequency of leukonychia among group A than group B. Non-statistically significant difference was detected between the studied groups as regard other clinical symptoms including; scalp affection, splinter hemorrhage, red lunula, nail pitting, onycholysis, oil drop, subungual hyperkeratosis and longitudinal ridge.

Table (3): Clinical presentation of the studied groups

	Group A		Group B		Test of significance
	N=20	%	N=20	%	
Scalp affection -ve +ve	 11 9	 55.0 45.0	 8 12	 40.0 60.0	 χ^2=0.902 P=0.342
Nail crumbling -ve +ve	 9 11	 45.0 55.0	 16 4	 80.0 20.0	 χ^2=5.23 P=0.02*
Splinter hemorrhage -ve +ve	 18 2	 90.0 10.0	 19 1	 95.0 5.0	 FET P=1.0
Red lunula -ve +ve	 18 2	 90.0 10.0	 19 1	 95.0 5.0	 FET P=1.0
Leukonychia -ve +ve	 16 4	 80.0 20.0	 20 0	 100.0 0.0	 FET P=0.106
Nail pitting -ve +ve	 12 8	 60.0 40.0	 11 9	 55.0 45.0	 χ^2=0.102 P=0.749
Onycholysis -ve +ve	 8 12	 40.0 60.0	 10 10	 50.0 50.0	 χ^2=0.404 P=0.525
Oil drop -ve +ve	 9 11	 45.0 55.0	 7 13	 35.0 65.0	 χ^2=0.417 P=0.519
Subungual hyperkeratosis -ve +ve	 14 6	 70.0 30.0	 15 5	 75.0 25.0	 χ^2=0.125 P=0.723
Longitudinal ridges -ve +ve	 19 1	 95.0 5.0	 20 0	 100.0 0.0	 FET P=1.0

χ^2: Chi-Square test, FET: Fischer exact test, *: Statistically significant.

Table (4) illustrates that among both groups A and B; there was a statistically significant decrease of NAPSI score after treatment. Higher percent of change was detected for group A than group B without statistically significant difference between studied groups.

Table (4): Comparison of NAPSI between before and after treatment

NAPSI	Group A N=20	Group B N=20	Test of significance (Mann Whitney U test)
Before treatment Mean ± SD	5.05±2.09	4.45±1.79	Z=0.866 P=0.452
After treatment Mean ± SD	2.20±2.14	2.85±2.66	Z=0.834 P=0.404
Wilcoxon signed rank	0.003*	0.007*	
% of change	56.4%	35.9%	Z=1.3 P=0.209

Z: Wilcoxon signed rank test, *: Statistically significant

Table (5) demonstrates no statistically significant difference between the studied groups concerning improvement frequency.

Table (5): Improvement frequency and improvement rate among the studied groups.

	Group A		Group B		Test of significance
Improvement	N=20	%	N=20	%	
No improvement	8	40.0	12	60.0	χ^2=1.60
Improvement	12	60.0	8	40. 0	P=0.206

χ2; Chi-Square test

Table (6) demonstrates that there was no statistically significant difference between studied groups concerning onset of improvement.

Table (6): Onset of improvement of the improved cases

Onset of improvement	Group A		Group B		Test of significance
	N=12	%	N=8	%	
1 month	3	25	1	12.5	
2 months	6	50	4	50	MC=2.42
4 months	3	25	1	12.5	P=0.490
6 months	0	0	2	25	

DISCUSSION

Psoriasis is a T helper 1 (Th1)/Th17-mediated, chronic inflammatory systemic disorder with phenotypic affection of skin, nail, joints, and entheses [(7)]. NP represents about 10% to 82% of psoriatic cases and is one of the most prevalent and challenging psoriasis sites to treat. In about 7.5% of cases, NP manifests in the absence of skin manifestations [(8,9)] and could be accompanied by pain, esthetic issues, and impairment of finger function which could substantially affect the patient's QoL [(10)].

Poor penetration of the topical agent across the nail and pain-related intralesional injections has been considered the main treatment difficulties. Topical and injectable treatment modalities are suggested for NP with few nails included. Systemic treatment such as biological therapy could be prescribed for cases with resistant nail diseases, cases with impairment of QoL, and cases with extensive skin and joint affection [(11)]. Considerable advancement has been made in proper recognition of the pathogenesis of psoriatic skin and joint diseases, and a lot of talented therapeutic modalities are now available for the management of severe PV. On the other hand, NP researches are limited, may be associated with the undertreatment of NP, which is a considerable unmet need in the treatment of psoriatic how reported that the immunosuppressive effects of tacrolimus ointment of 0.1% and 0.03 % have been shown to be beneficial in terms of NP treatment [(12)].

Calcineurin stimulates T-cells by upregulation of the expression of IL-2. Increase in IL-2 triggers the differentiation of T cell response [(12)]. Suppression of calcineurin could be considered as an efficient therapeutic modality in the context of plaque psoriasis [(13)]. Unlikely, the utilization of systemic calcineurin inhibitors is restricted owing to their major adverse events; on the other hand, topical use of calcineurin

inhibitors may limit most of these adverse events [11]. Although topical cyclosporin was found successful in management of nail psoriasis, the poor penetration of topical cyclosporin across the skin and nail structures owing to its lipophilic nature and size of the molecule added difficulty to its use [14].

Tacrolimus is another calcineurin inhibitor but possess a much better skin-penetrating capacities compared to cyclosporine [11]. Two concentrations of topical tacrolimus are available: 0.1% and 0.03%. All the available trials on topical tacrolimus for treatment of nail psoriasis were done using the higher concentration (0.1%), which is more expensive and frequently not available in many developing countries. Topical tacrolimus was proved to be safe by its two concentrations in atopic child aged 1 year and older [15].

The present comparative study aimed to evaluate topical tacrolimus in both available concentrations for their efficiency, safety and affordability in treatment of nail psoriasis. Forty cases with NP were comprised in the study. The cases were haphazardly divided into two equal groups: group A treated by (Tacrolimus 0.1%) and Group B treated by (Tacrolimus 0.03%). There was no significant difference between studied groups with regard to existence of skin lesion and presence of medical co-morbidities including psoriatic arthropathy, thus no factors can affect the results.

Psoriatic arthropathy was detected among 15% and 35% for group A and B respectively. The recorded prevalence of NP in cases with psoriatic arthritis (PsA) has differed among studies, from 32–97% (average 66%) [16]. After the follow-up period has ended, improvement percentage as measured by NAPSI was 60% among group A versus 40% of Group B with no statistically significant difference between two groups (p=0.206). Also, there was no statistically significant difference between studied groups as regard onset of improvement. Clinical improvement started after one month in 3 cases in group A (25%) and one case in group B (16.7%) with further improvement in the follow-up period of six months and the change wasn't significant (P=0.490).

The present study showed that statistically significant decrease of NAPSI score after treatment was observed in the two studied group (Wilcoxon signed rank 0.003 and 0.007 for group A and B respectively) although the improvement was more significant in group A than group B, but the difference was not significant (P=0.209).

In the present study, evaluation by NAPSI score after 6 months in group A revealed complete clearance of nail lesions in 40% of cases (8 cases), partial improvement among 20% (4 cases), and no improvement in 40% of cases (8 cases). Among group B, we found complete clearance of nail lesion in 30% of cases (6 cases) and partial improvement in 10% of cases, no improvement in 60% of cases (12 cases). Although the improvement was more evident in group A, but the difference was non-significant (P=0.206). Improvement was observed not only in nail matrix signs of NP (pitting, leukonychia, and crumbling nail plate) but also in nail bed signs (hyperkeratosis, onycholysis, and oil-drop discoloration).

In line with our findings **De Simone *et al.*** [5], in a twelve-week study to evaluate the efficiency and safety of topical tacrolimus 0.1% ointment in 21 cases with NP, they reported that the degree of NP improved significantly, as assessed by NAPSI (−57 %) and target NAPSI (−65 %) and found that tacrolimus ointment was of comparable effectiveness on nail bed and nail matrix features so they considered topical tacrolimus 0.1% ointment as a promising therapeutic line for NP.

The finding in this study that tacrolimus in a lower concentration (0.03%) is also effective in treating of nail psoriasis was reported by **Tweer *et al.*** [17], who reported that the immunosuppressive effects of tacrolimus ointment of 0.1% and 0.03 % have been shown to be beneficial in the treatment of NP.

It has been proposed that nail growth rate is increased by PV because keratinocyte proliferation and cell turnover are accelerated in cutaneous psoriasis plaques in comparison with normal skin [18]. In the current study we are reporting an interesting finding that although the rate of nail growth in psoriatic cases is reported to be increased to about 4.4 millimeter per month, in the present study we found that the rate of nail growth in cases with NP under topical calcineurin inhibitor therapy was normalized to be 3.6 mm per month.

It was found that topical calcineurin inhibitor is similarly efficient on nail bed and matrix psoriatic lesions. Tacrolimus ointment has been demonstrated to efficiently manage a number of other nail dystrophies, comprising nail lichen planus, median canaliform atrophy, and paronychia, when it is applied without the use of occlusive medication systems. This is likely due to the drug's lipophilicity and formulation in the ointment [19-21].

As regard side effects, the present study showed that no significant side effects to topical calcineurin inhibitors unlike other topical treatment modalities used for nail psoriasis. This comes in accordance with **Malecic and Young** [22] who reported that topical tacrolimus forms have gained much compliance in psoriatic cases. The commonest adverse events recorded in previous studies involved mild itching and a warmth felt at the application site in the beginning of the therapy, which diminished by continuation of therapy. **De Simone *et al.*** [5] recorded a single case of acute paronychia which induced drug withdrawal.

In conclusion, there are data, including our results, supporting the efficacy of topical tacrolimus by either concentration (0.1% and 0.03%) in successful treatment of nail psoriasis. Topical preparations, particularly, take numerous months to demonstrate

efficiency and it is difficult to adhere to therapy for several months. As a result, topical therapy is limited by penetration into the nail and adherence to lengthy therapeutic modalities lasting months. It could be beneficial and encouraging to include a suitable transdermal delivery aiding material to try to shorten the time to get improvement.

Limitations: The main limitations of our study involve cost of treatment and low socioeconomic level of the patients, poor compliance on treatment by the patients and long period before nail improvement. Finally, all cases were recorded from a single center.

CONCLUSION

Our comparative clinical study exhibited that both concentrations of topical calcineurin inhibitors (0.1% and 0.03%) showed high statistically significant improvement in nail psoriasis after six months of treatment. Additionally topical calcineurin inhibitors demonstrated no side effects, so they are safe and tolerable drugs in nail psoriasis treatment.

The obtained results suggest that topical tacrolimus 0.1% and 0.03% can be talented therapies in the context of NP treatment.

Conflicts of interest: None.
Funding: None.

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